REMARKS

Applicants thank the Examiner for the telephone call on June 14, 2011. In accordance with the Examiner's request[2], Applicants have combined the content of the Amendment and Response to Non-Final Office Action filed March 10, 2011 with the content of the Supplemental Amendment filed on April 26, 2011.

Claims 126-128, 131, 144, 149, 150, 157 and 159-164 were pending in the application at the time of issuance of the Non-Final Office Action mailed November 10, 2010. Claims 126, 128, 144 and 160-164 have been amended and new claims 165-172 have been added. Accordingly, upon entry of the amendments presented herein, claims 126-128, 131, 144, 149, 150, 157, and 159-172 will remain pending in the application.

Support for the amendments to the claims may be found throughout the specification and claims as originally filed. In particular, support for amendments to claims 126, 144, 163 and 164 may be found at, for example, page 4 lines 7-13 of the specification. Additional support for amendments to claims 126 and 144 may be found at, for example, page 8 line 14 of the specification.

Support for new claim 165 may be found at, for example, page 55 lines 16-27, page 40 lines 12-15, Figure 2A, page 43 lines 4-8, and Figures 7B and 7C of the specification.

Support for new claim 166 may be found at, for example, page 57 lines 16-27, Figure 10, and page 19 line 18 of the specification.

Support for new claims 167-171 may be found at, for example, page 6 lines 15-18 and Figure 1A.

No new matter has been added. Amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely in the interest of expediting prosecution and allowance of the pending claims. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

[2] In accordance with 37 C.F.R. § 1.704(c)(8), the Patent Term of a patent shall be reduced where Patentee submits a supplemental reply or other paper, not expressly requested by the Examiner, after a reply has been filed. As the Examiner has expressly requested that Applicants submit this Supplemental Amendment, Applicants should not be subject to a reduction of Patent Term when this application issues as a patent.

Acknowledgment of Examiner's Withdrawal of Previous Rejections

Applicants gratefully acknowledge the Examiner's withdrawal of the following: (a) the previous rejection of claim 128 under 35 U.S.C. § 112, second paragraph, (b) the previous rejection of claim 144 under 35 U.S.C. § 112, second paragraph, and (c) the previous rejection of claims 126-128, 131, 144, 149, 150, 157 and 159 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification

The Examiner has maintained the objection to the specification made in paragraph 11 of the Office Action mailed 01/05/2010 with regard to claim 128. Claim 128, before the current amendment, claimed a method of resuscitating dormant moribund or latent *Mycobacterium tuberculosis* bacterial cells according to claim 126 or claim 127, wherein said bacterial cells are present in a sample, and the method identifies dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells in the sample by detecting growth of *Mycobacterium tuberculosis* bacterial cells in the sample. In the Office Action mailed 01/05/2010 the Examiner stated that there is no antecedent basis for a method of resuscitating dormant moribund or latent *Mycobacterium tuberculosis* bacterial cells according to claim 126 or claim 127, wherein the resuscitating method concurrently serves as a method of specifically identifying dormant moribund or latent *Mycobacterium tuberculosis* bacterial cells in a generic sample, or in a sample from a human or an animal.

This objection has two parts. First, the Examiner questions whether there is support for a resuscitation method that concurrently serves as a method of specifically identifying dormant, moribund or latent *Mycobacterium tuberculosis* cells. The claim has been amended to include high G+C Gram-positive bacterial cells, of which *Mycobacterium tuberculosis* cells are one example. The specification provides support for a method that serves concurrently to resuscitate and identify dormant, moribund or latent high G+C Gram-positive bacterial cells (including *Mycobacterium tuberculosis* cells). The specification explains that bacteria, including pathogenic mycobacteria such as *Mycobacterium tuberculosis*, can enter a latent or dormant state that complicates the detection, cultivation and enumeration of bacteria, for example, in the food and healthcare industries (see specification at page 2 line 22 to page 3 line 14). The specification defines RP factors as encompassing substances capable of resuscitating dormant, moribund or latent cells (e.g., bacterial cells) (page 4 lines 5-7). In addition, the specification at page 2 lines

24-28 states that resuscitation permits "non-culturable" dormant, moribund, or latent cells to become culturable. Thus, the specification explains that one of skill in the art can identify the presence of dormant, moribund or latent bacterial cells by demonstrating renewed culturability (i.e., by detecting growth following incubation in culture medium) of such dormant, moribund, or latent cells following contact of a sample containing such cells with an RP factor.

Second, the Examiner questions whether there is support for employing a generic sample, or a sample taken from a human or animal. The specification states that the term "sample" includes samples taken from various sources, including a human or animal (see specification, e.g., at page 18 line 26) as well as soil, food, marine, freshwater, or tissue samples (see specification, e.g., at page 18 lines 25-26) and product samples, such as, for example, samples of a foodstuff, pharmaceutical preparation, or medical product (see specification, e.g., at page 31 lines 15-19). Thus, there is support in the specification for employing a sample derived from a human or animal.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this objection to the specification.

Rejection of Claim 128 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has maintained the rejection made in paragraph 29(a) of the Office Action mailed 01/05/10, wherein the Examiner had rejected claim 128 as allegedly being indefinite under 35 U.S.C. § 112, second paragraph. The Examiner stated that

> [i]t is unclear how a method of resuscitating a dormant, moribund or latent Mycobacterium tuberculosis cells comprising contacting the dormant, moribund or latent Mycobacterium tuberculosis cells present in a sample in vitro and incubating the cells in culture medium containing the polypeptide ends up being a method of identifying specifically "a dormant, moribund or latent Mycobacterium tuberculosis cell in the sample."

Solely in the interest of expediting prosecution and in no way acquiescing to the validity of the Examiner's rejection, claim 128 has been amended to state that the method identifies "the presence of dormant, moribund or latent high G+C Gram-positive bacterial cells in the sample by detecting growth of high G+C Gram-positive bacterial cells in the sample." This amendment renders the rejection moot and Applicants respectfully request that the rejection be reconsidered and withdrawn.

Notwithstanding the foregoing, Applicants wish to make the following remarks of record. Applicants respectfully traverse this rejection for at least the following reasons. Applicants respectfully submit that, based on the teachings in the specification as well as the knowledge generally available in the art at the time the application was filed, a skilled artisan would find it clear that a method of resuscitating dormant, moribund or latent bacterial cells comprising contacting the dormant, moribund or latent bacterial cells present in a sample in vitro with the polypeptide of claim 126 or 127 and incubating the cells in culture medium containing the polypeptide of claim 126 or 127, would provide a method of identifying the presence of dormant, moribund or latent bacterial cells in the sample. The specification provides descriptive support for a method that serves to concurrently resuscitate and identify dormant, moribund or latent bacterial cells. For example, the specification at page 2 lines 24-28 states that resuscitation permits "non-culturable" dormant, moribund, or latent cells to become culturable. Thus, one of skill in the art can identify the presence of dormant, moribund or latent bacterial cells by demonstrating renewed culturability of these cells following contact of a sample containing such cells with an RP factor, such as the polypeptide of claim 126 or 127. In view of the foregoing teachings in Applicants' specification and the clear language of the claims, one of skill in the art would find claim 128 to be clear and definite. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claim 159 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has maintained the rejection of claim 159 made in paragraph 29(c) of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because it depends from claim 128 (note that this rejection was actually made in paragraph 29(d)). The Examiner's indefiniteness rejection of claim 128 has been addressed above. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 159 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 126-128, 131, 144, 149, 150, 157 and 159 Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner has rejected claims 126-128, 131, 144, 149, 150, 157 and 159 under 35 U.S.C. §112, first paragraph, as allegedly containing inadequate written description. The Examiner stated that

> "[t]he description of a single species having the required function within the recited broad genus is not sufficient to support the patentability of the genus under 35 U.S.C. § 112, first paragraph. See *University of California v. Eli Lilly & Co.*, 199 F.3d 1559, 1567, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). The instant specification does not disclose which 5% of amino acid residues should be changed within the single disclosed polypeptide species of SEQ ID NO: 2 in order to maintain the required biological functions, i.e., the functional capacity to resuscitate dormant, moribund or latent *M. tuberculosis* cells *in vitro* in a culture medium or a human or animal sample, upon performing the recited steps and/or having the ability to identify a dormant, moribund or latent *M. tuberculosis* cell in the sample by detecting growth of bacterial cells in the sample."

Solely in the interest of expediting prosecution and in no way acquiescing to the Examiner's rejection, claim 126 has been amended to be directed to a method of stimulating growth of high G+C Gram-positive bacterial cells or of resuscitating dormant, moribund or latent high G+C Gram-positive bacterial cells, the method comprising (i) contacting high G+C Gram-positive bacterial cells or dormant, moribund or latent high G+C Gram-positive bacterial cells in vitro with an isolated polypeptide having at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO:2, wherein said polypeptide is capable of stimulating growth of high G+C Gram-positive bacterial cells or resuscitating a dormant, moribund, or latent high G+C Gram-positive bacterial cells; and (ii) incubating said high G+C Gram-positive bacterial cells or said dormant, moribund or latent high G+C Gram-positive bacterialcells in culture medium containing the polypeptide, thereby stimulating growth of said high G+C Gram-positive bacterial cells or resuscitating said dormant, moribund or latent high G+C Gram-positive bacterial cells. Similar amendments have been made to the other independent claims.

Applicants respectfully traverse this rejection on the grounds that the instant specification sufficiently describes the claimed invention such that a skilled artisan would recognize that Applicants were in possession of the claimed invention at the time of filing. An objective standard for determining compliance with the written description requirement under 35 U.S.C. § 112, first paragraph, is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicants were in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117

(Fed. Cir. 1991) and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1615, 1618 (Fed. Cir. 1989). In the present case, the specification discloses ***at least ten species falling within the claimed genus***, i.e., ten amino acid sequences that have at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO:2 (including, e.g., SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, and SEQ ID NO:43), and ***working examples demonstrating that species falling within the claimed genus possess the claimed resuscitating and growth stimulating function***.

Applicants demonstrated the functional capacity of an RP factor purified from the supernatants of succinate-grown *Micrococcus luteus* cells (See, e.g., page 49 lines 6-16 and Figure 3B (resuscitation shown by MPN assay); Figure 4A (concentration-dependence of resuscitation shown by MPN assay); Figure 4B(stimulation of growth shown by plating); Figures 3D, 6B and Table 1 (reduction of apparent lag phase); and page 52 lines 9-24). Applicants obtained microsequences of this RP factor, from which they designed PCR primers that were used to amplify a 147 bp fragment of *M. luteus* DNA that was cloned and sequenced (see, e.g., page 49 line 25 to page 50 line 6 of the specification). Using this fragment a BLAST search was undertaken and the predicted amino acid sequence of the RP factor-encoding gene was determined (see the specification, e.g., at page 50 lines 10-11, Figure 2A and page 40 lines 11-15). The N-terminal residues of the predicted sequence (SEQ ID NO:36) agreed with the protein microsequence data, including residues not used in primer design (See, e.g., Figure 2A and page 50 lines 1-2 of the specification).

In addition, Applicants created a recombinant version of *M. luteus* RP factor, which corresponds to the secreted form of RP-factor, the sequence of which is given in Figure 2A as SEQ ID NO:43, which is identical to the portion of SEQ ID NO:36 from A39 onward (see, e.g., the specification at page 55 lines 16-17 and page 40 lines 12-15). The recombinant secreted protein also showed the expected functional capacity (see, e.g., the specification at page 55 lines 21-27, Figure 7B, and Figure 7C).

Further, Applicants created a recombinant protein based on a *Mycobacterium tuberculosis* RP factor identified in the BLAST search. This protein was the secreted version of *M. tuberculosis* RP factor, which corresponds to GI: 1655671 starting at residue D50, as stated in the specification at page 57 lines 18-19. The sequence of GI: 1655671 is disclosed in the

specification as SEQ ID NO:7. The secreted version of the protein encoded by SEQ ID NO:7 also demonstrated functionality (see, e.g., the specification at page 57 lines 23-27 and Figure 10).

Applicants would like to note that in the Supplemental Amendment after Final Action dated 07-13-2010, the previous attorney of record stated that the recombinant *M. tuberculosis* RP factor was a fragment of SEQ ID NO:2 and included amino acids 117-184 of SEQ ID NO:2. In fact, as explained above, this RP factor was a fragment of SEQ ID NO:7, which showed similarity with amino acids 117-184 of SEQ ID NO:2 but did not comprise exactly this sequence.

In summary, Applicants demonstrated the functionality of a purified RP factor, a recombinant version of *M. luteus* RP factor, and a recombinant *M. tuberculosis* RP factor. The fact that each of these showed functionality demonstrates a predictable correlation between structure and function. Moreover, the Examiner acknowledges that Applicants have identified conserved structural features of RP factors that are likely to be functionally important, stating that "Applicants' specification clearly provides guidance relating to those regions of the protein where sequence variations are likely to be tolerated and those conserved regions where variations in the sequence are less desirable." The specification provides information regarding conserved amino acids and protein structures, for example, at page 51 line 8 to page 52 line 5, as well as Figure 1A and Figure 9. Thus, a structure-function correlation is present in the context of the present invention.

Where a structure-function correlation is present, as is the case here, even one functional species within a polypeptide genus can suffice to satisfy the written description requirement. See Example 11B, Claim 2, pages 39-42 of the *Written Description Training Materials*, (published March 25, 2008; http://www.uspto.gov/web/menu/written.pdf; hereinafter referred to as the "Guidelines"). The present case is similar to Claim 2 of Example 11 of the Guidelines, where the claim was to "an isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO:2; wherein the polypeptide has activity Y." The Guidelines note that based on the disclosure of SEQ ID NO:2 and the knowledge in the art, one of skill in the art could identify and routinely generate all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO:2. Similarly, here, based on the disclosure of amino acid residues 117 to 184 of SEQ ID NO:2 and the knowledge in the art, one of skill in the art could identify and routinely generate all of the polypeptides with at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO:2. Furthermore, one

of skill in the art could predict which sequence variations would likely interfere with the claimed function based on the guidance in the disclosure as well as based on knowledge in the art about conservative substitution and empirical similarities between amino acid residues. Example 11 of the Guidelines at page 38 notes,

> [f]or information on amino acid substitution exchange groups and empirical similarities between amino acid residues, see a standard text such as Schulz *et al.*, PRINCIPLES OF PROTEIN STRUCTURE, pp.14-16, Springer-Verlag (New York 1979). There is a limit to how much substitution can be tolerated before the original tertiary structure is lost. Generally, tertiary structure conservation would be lost when the amino acid sequence varies by more than 50%. See, *e.g.*, Cyrus Chothia and Arthur M. Lesk, "The relation between the divergence of sequence and structure in proteins," 5 THE EMBO JOURNAL 823-26 (1986).

Further, using techniques known in the art as well as methods described in the specification, one of skill in the art could test polypeptides for the ability to resuscitate dormant, moribund or latent bacterial cells (see, e.g., the specification, at page 45 line 16 to page 46 line 10; page 58 line 4 to page 59 line 19; and Figures 3, 4, 6, 7, 8, and 10). Thus, the written description provided shows that Applicants were in possession of the invention at the time of filing. More importantly, it should be noted that the written description provided in the present case is much stronger than the written description provided for Claim 2 in Example 11B of the Guidelines, because ***Applicants have described at least ten species that fall within the claimed genus and have demonstrated that species falling within the claimed genus possess the claimed resuscitating and growth stimulating function***.

One of the factors to be used in determining the adequacy of written description is predictability of the aspect at issue. See, e.g., *Ariad Pharmaceuticals v. Eli Lily*, 560 F.3d 1368, 1372. As further evidence of predictability, Applicants submit additional post-filing evidence which demonstrates the functional capacity of five species that fall within the claimed genus (i.e., Rpf A, Rpf B, Rpf C, Rpf D). Evidence demonstrating the functional capacity of Rpf D, which corresponds to the secreted version of SEQ ID NO:7, was also described in the specification, as discussed above. The additional evidence for functional capacity of claimed species is described in the following publications: Mukamolova, G.V. et al. *Molecular Microbiology* 46: 623-635 (2002) and Zhu et al. *Tuberculosis*, 83, 261-269 (2003), copies of

which are included herein as Appendices A and B for the Examiner's convenience. Mukamolova et al. demonstrated the functional capacity of Rpf A, Rpf C, Rpf D, and Rpf E, which correspond to the secreted forms of the polypeptides SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:2 (i.e., the forms lacking signal sequences or N-terminal trans-membrane helices/anchors). Similarly, Zhu et al. demonstrated the functional capacity of the RpfB, which corresponds to the secreted version of SEQ ID NO:1. These five species are disclosed in the specification, for example, at page 6 lines 15-18 and Figure 1A.

In view of the foregoing, it is evident that the Applicants were in possession of the claimed invention at the time of filing. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 128, 144, 159, and 162-164
Under 35 U.S.C. § 112, First Paragraph (New Matter)

The Examiner has rejected claims 128, 144, 159, and 162-164 under 35 U.S.C. § 112 as allegedly containing new matter.

First, the Examiner requests that Applicants point to specific parts of the as-filed specification that support a method of resuscitating dormant, moribund or latent *Mycobacterium tuberculosis* cells comprising contacting the dormant, moribund or latent *Mycobacterium tuberculosis* cells present in a sample in vitro and incubating the cells in culture medium containing the polypeptide that also serves as a method of identifying specifically 'a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in the sample by detecting the growth of bacterial cells in the sample.' Applicants respectfully submit that the amendments to claims 128, 144, and 162-164 render this rejection moot.

Nonetheless, Applicants wish to make the following remarks of record. The specification provides support for a method that serves concurrently to resuscitate and identify dormant, moribund or latent high G+C Gram-positive bacterial cells (including *Mycobacterium tuberculosis* cells). The specification explains that bacteria, including pathogenic mycobacteria such as *Mycobacterium tuberculosis*, can enter a latent or dormant state that complicates the detection, cultivation and enumeration of bacteria, for example, in the food and healthcare industries (see specification at page 2 line 22 to page 3 line 14). The specification defines RP factors as encompassing substances capable of resuscitating dormant, moribund or latent cells

(e.g., bacterial cells) (page 4 lines 5-7). In addition, the specification at page 2 lines 24-28 states that resuscitation permits "non-culturable" dormant, moribund, or latent cells to become culturable. Thus, the specification explains that one can identify the presence of dormant, moribund or latent bacterial cells by demonstrating renewed culturability (i.e., by detecting growth following incubation in culture medium) of such dormant, moribund, or latent cells following contact of a sample containing such cells with an RP factor.

Second, the Examiner states that a generic cell 'strain' expressing a nucleic acid encoding the recited polypeptide has no support in the specification. Applicants respectfully submit that, contrary to the Examiner's assertions, such support is present in the specification. For example, at page 25 lines 16-19, the specification states that

> [t]he invention also contemplates recombinant RP-factor. As used herein, the term "recombinant" is intended to define material which has been produced by that body of techniques collectively known as "recombinant DNA technology" (for example, using the nucleic acid, vectors and/or host cells described infra).

Further, at page 29 line 30 to page 30 line 1, the specification describes the "host cells" of the invention, stating that "[a]ny suitable host cell may be used, including prokaryotic host cells (such as *Escherichia coli*, *Streptomyces* spp. and *Bacillus subtilis*) and eukaryotic host cells." The fact that the specification contemplates that "[a]ny suitable host cell may be used" provides support for a generic cell strain.

In view of the foregoing teachings in the Applicants' specification it is clear that literal as well as implicit support exists in the specification for claims 128, 144, 159, and 162-164. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 128, 144 and 162 as allegedly being indefinite under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants thank the Examiner for the suggestions of how to respond made in paragraph 22 (a) - (c) of the Office Action. Applicants have amended claims 128, 144 and 162 in line with these suggestions.

The Examiner states that claim 162, as well as claims 128 and 159, are indefinite and confusing in the limitations 'the method identifies dormant, moribund or latent Mycobacterium tuberculosis bacterial cells in the sample by detecting growth of bacterial cells in the sample.'

Solely in the interest of advancing prosecution and without acquiescing to the rejection, claim 162 has been amended to be directed to a method in which the dormant, moribund or latent high G+C Gram-positive bacterial cells are present in a sample, and the method identifies the presence of dormant, moribund or latent high G+C Gram-positive bacterial cells in the sample by detecting growth of high G+C Gram-positive bacterial cells in the sample. Similar amendments have been made to claims 128 and 159. Applicants respectfully submit that these amendments render the rejections moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 449-6512.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-4876, under Order No. 118160-00301.

Dated: June 14, 2011

Respectfully submitted,

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